Pheromone Synthesis, CLXXVIII[◇]

Synthesis of (−)-*exo*-Isobrevicomin and Its (−)-*endo* Isomer, the Components of the Male-Produced Volatiles of the Mountain Pine Beetle, *Dendroctonus ponderosae*

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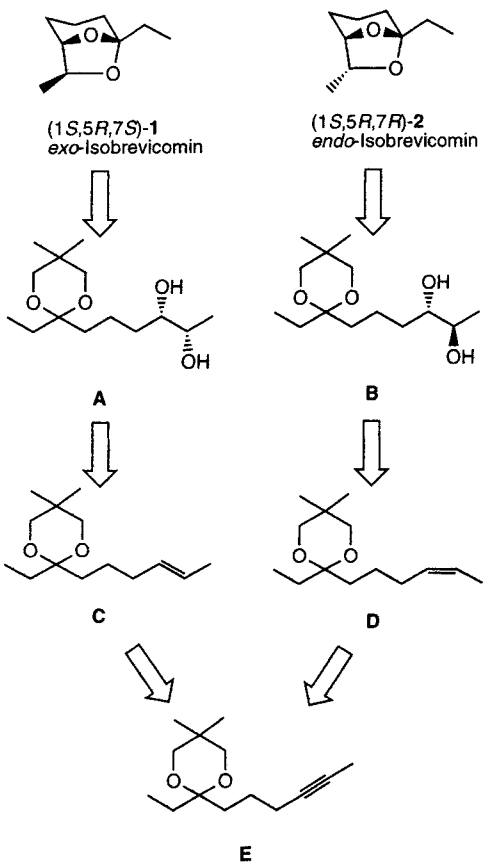
(−)-*exo*-Isobrevicomin {(1*S*,5*R*,7*S*)-(−)-5-ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane (**1**)} and its (−)-*endo* isomer [(1*S*,5*R*,7*R*)-**2**] were synthesized by employing the acetylenic acetal **7** as the common intermediate and by using the Sharpless asymmetric dihydroxylation and lipase-catalyzed acetylation as the key reactions.

Both the *exo* and *endo* isomers of isobrevicomin (**1** and **2**) were isolated in 1996 by Francke et al. as the components of the volatiles obtained from male mountain pine beetles, *Dendroctonus ponderosae*[1]. The *exo* isomer (**1**) was far more abundant in the volatiles. Francke et al. synthesized (1*S*,5*R*,7*S*)-**1** by starting from (+)-tartaric acid, and their coinjection experiments by chiral GC of the natural and synthetic **1** revealed the natural *exo*-isobrevicomin to be the (1*S*,5*R*,7*S*) isomer of at least 90% e.e.[1]. The naturally occurring *endo*-isobrevicomin may share the same, stereochemically equivalent (1*S*,5*R*)-6,8-dioxabicyclo[3.2.1]octane skeleton as shown in **2**, but this has yet to be proved. According to the suggestion of Francke, we undertook our project to synthesize both (1*S*,5*R*,7*S*)-**1** and (1*S*,5*R*,7*R*)-**2** by employing a chemical or an enzymatic asymmetric reaction.

Scheme 1 shows our retrosynthetic analysis of **1** and **2**. Isobrevicomins **1** and **2** can be prepared by deprotection and intramolecular acetalization of the dihydroxy acetals **A** and **B**, respectively. The diols **A** and **B** are obtained by the Sharpless asymmetric dihydroxylation (AD)[2,3] of the (*E*)- and (*Z*)-olefinic acetals **C** and **D**. If the enantiomeric purity of **A** and **B** is low and unsatisfactory, it may be improved by either chemical or enzymatic purification. Both **C** and **D** can be prepared by selective reduction of the acetylenic acetal **E**.

Two different syntheses of the building block **7** (= **E**) are summarized in Scheme 2. Commercially available 3-pentyn-1-ol (**3**) was converted to the corresponding iodide **4** via the tosylate. Alkylation of methyl 3-oxopentanoate with **4** yielded the β-oxo ester **5**, which was hydrolyzed and decarboxylated to give 7-nonyn-3-one (**6**). Acetalization of **6** with

Scheme 1. Retrosynthetic analysis of **1** and **2**



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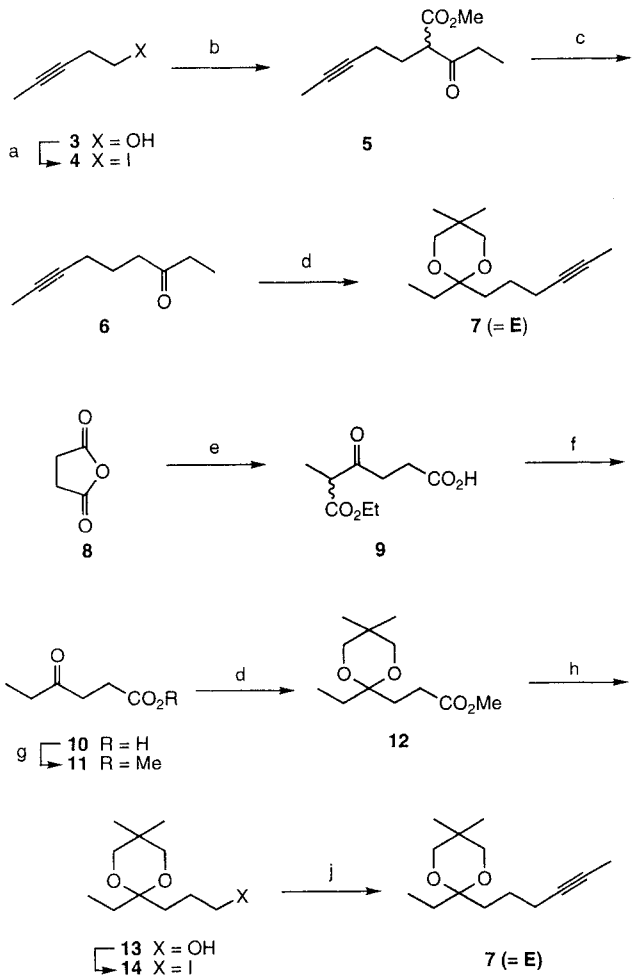
2,2-dimethylpropane-1,3-diol furnished the acetylenic acetal **7** (= **E**). The overall yield of **7** was 41% based on **3** (5 steps). The second synthetic route to **7** started from succinic anhydride (**8**). Treatment of **8** with ethyl 2-bromopropanoate and zinc/copper couple[2] gave the β-oxo ester **9**, which was hydrolyzed and decarboxylated to give 4-oxohexanoic acid (**10**). The corresponding methyl ester **11** was acetalyzed to afford **12**, whose reduction with lithium tetrahydridoaluminate furnished the alcohol **13**. The corresponding iodide **14** was treated with lithium propynide to yield the acetylenic acetal **7** (= **E**). This route was less efficient than the first one, and the overall yield of **7** was 11% based on **8** (8 steps).

Scheme 2. Synthesis of the building block **7** (= **E**)



Reagents: (a) i) TsCl, C_5H_5N; ii) NaI, Me_2CO (85%). – (b) Methyl 3-oxopentanoate, K_2CO_3, Me_2CO, DMF (57%). – (c) LiOH, $MeOH/H_2O$ (91%). – (d) 2,2-Dimethyl-1,3-propanediol, TsOH · H_2O, C_6H_6 (94% for **7**; 70% for **12**). – (e) Zn/Cu, $MeCHBrCO_2Et$, DMF. – (f) HCl, H_2O. – (g) MeOH, H_2SO_4 (19% based on **8**). – (h) $LiAlH_4$, Et_2O (99%). – (i) i) TsCl, C_5H_5N; ii) NaI, $NaHCO_3$, Me_2CO (85%). – (j) MeC≡CH, *n*BuLi, HMPA/THF (70%).

Conversion of **7** to the target molecules **1** and **2** is summarized in Scheme 3. For the preparation of (1*S*,5*R*,7*S*)-*exo*-isobrevicomin (**1**), the acetylenic acetal **7** was reduced with lithium in ethylamine to give the (*E*)-alkene **15**. Asymmetric dihydroxylation[3,4] of **15** with AD-mix-α® furnished the diol **16** in 94% yield. The enantiomeric purity of **16**, however, was only 77% e.e. as determined by HPLC analysis of the corresponding bis-(*R*)-α-methoxy-α-trifluofomethylphenylacetate (MTPA ester). In order to enhance the enantiomeric purity of **16**, it was derivatized to the corresponding bis(3,5-dinitrobenzoate) **17**. The crystalline **17** was recrystallized twice to give pure **17**, melting at 129–131 °C. Treatment of the purified **17** with potassium carbonate in methanol regenerated pure **16** (99% e.e.). Dilute hydrochloric acid converted **16** to (1*S*,5*R*,7*S*)-*exo*-isobrevicomin (**1**), $[\alpha]_D^{22} = -60.4$ ($CHCl_3$). The overall yield of **1** was 32% based on **7** (5 steps).

The synthesis of (1*S*,5*R*,7*R*)-*endo*-isobrevicomin (**2**) was somewhat more complicated than that of **1**. Semihydrogenation of **7** was executed according to Choi and Yoon[5] over nickel boride (Ni_2B) prepared on borohydride exchange resin (BER) in methanol, under hydrogen, to give **18**. The (*Z*) selectivity realized by Choi and Yoon's procedure was over 95%, even when the reaction was carried out on a large scale, using an amount of nickel diacetate only 80% of that recommended in their original report[5]. In our hands, large-scale hydrogenation of **7** sometimes gave a mixture of (*Z*)-**18** (80%) and its (*E*) isomer (20%) when Yoon's original procedure was exactly followed. The resulting (*Z*)-alkene **18** (>95% pure as judged by ^{13}C-NMR analysis) was submitted to asymmetric dihydroxylations[3,4] to give the diol **19** of no more than 15% e.e. as estimated by HPLC analysis of the corresponding bis[(*R*)-MTPA] ester. This diol **19** was successfully purified by the enzymatic method of Kim et al.[6]. Accordingly, vinyl acetate in the presence of immobilized lipase PS (Amano)[7] from *Pseudomonas cepacia* selectively acetylated **19** [(2*R*,3*S*)-diol] to give a mixture of **21** and **22**, leaving the enantiomeric diol **20** [(2*S*,3*R*)-diol] unacetylated. The acetylated products **21** and **22** were readily separable from the diol **20** by chromatography. The resulting mixture of **21** and **22** was treated with potassium carbonate in methanol to give **19** of 86% e.e. This was again subjected to the lipase PS catalyzed acetylation under the same conditions as before, to give a mixture of further enantiomerically enriched **21** and **22**, which yielded **19** of 98% e.e. Treatment of the purified **19** with dilute hydrochloric acid furnished (1*S*,5*R*,7*R*)-*endo*-isobrevicomin (**2**), $[\alpha]_D^{26} = -88.1$ ($CHCl_3$). The overall yield of **2** was 11% based on **7** (7 steps).

In conclusion, we have synthesized both (–)-*exo*-isobrevicomin (**1**) and its (–)-*endo* isomer (**2**). The absolute configuration of the naturally occurring *endo*-isobrevicomin will be clarified in due course by using (–)-**2** as the reference sample.

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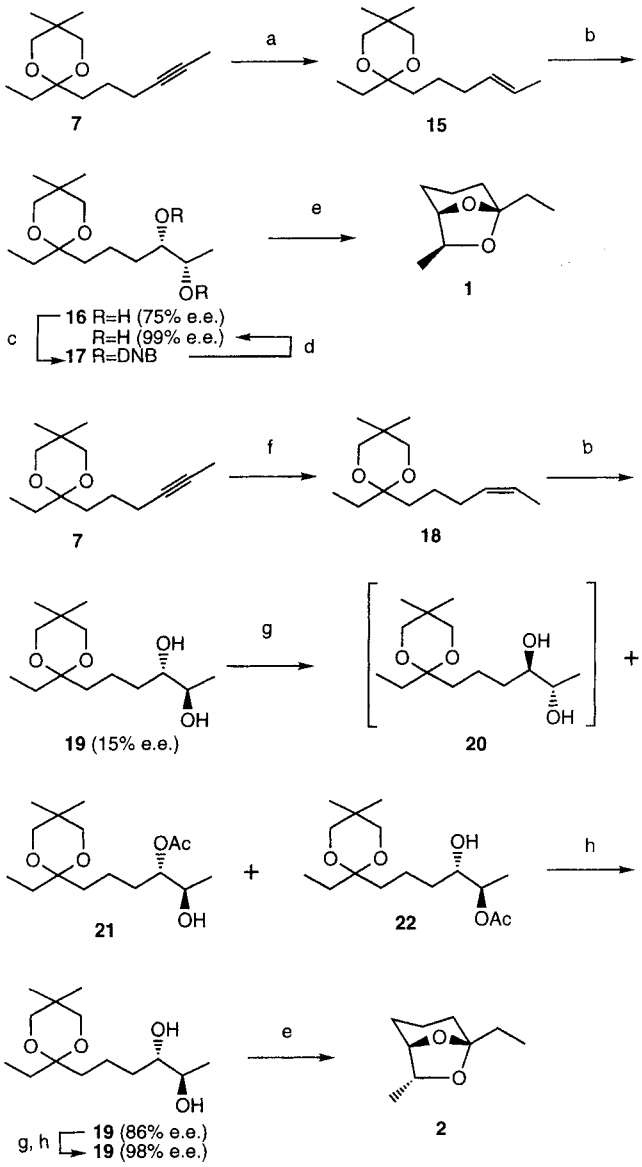
Scheme 3. Synthesis of **1** and **2**



Reagents: (a) Li, $EtNH_2$ (99%). – (b) AD-mix α®, $MeSO_2NH_2$, *t*BuOH, H_2O (94% for both **16** and **19**). – (c) 3,5-Dinitrobenzoyl chloride (DNBCl), C_5H_5N, CH_2Cl_2; recrystallization (59%). – (d) K_2CO_3, MeOH (92%). – (e) dild. HCl (64% for **1**; 28% for **2**). – (f) H_2, Ni_2B/BER, MeOH (97%). – (g) Immobilized lipase PS, CH_2=CHOAc, *t*BuOMe; chromatographic separation to give a mixture of **21** and **22**. – (h) K_2CO_3, MeOH [53% (15→86% e.e.); 77% (86→98% e.e.)].

Experimental Section

Boiling points and melting points; uncorrected values. – IR: Perkin-Elmer 1640. – ^{1}H NMR: Jeol JNM-EX 90A (90 MHz), Jeol JNM-EX 270L (270 MHz), Bruker DPX 300 (300 MHz) and Jeol GSX-500 (500 MHz) (TMS at δ = 0.00 or $CHCl_3$ at δ = 7.26 as an internal standard). – ^{13}C NMR: Jeol JNM-EX 90A (22.5 MHz), Jeol JNM-EX 270L (67.8 MHz, TMS as an internal standard). – MS: Hitachi M-80-B. – CC: Merck Kieselgel 60 Art 7734. – TLC: 0.25 mm Merck silica gel plates (60F-254).

1-Iodo-3-pentyne (**4**): *p*-Toluenesulfonyl chloride (16.6 g, 87.1 mmol) was added to an ice-cooled solution of **3** (4.37 g, 56.3 mmol) in dry pyridine (48 ml) at 0–4°C. The mixture was stirred at 4°C for 10 h, then poured into water and extracted with diethyl ether. The ethereal extracts were washed with satd. copper(II) sulfate solution, water, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo to give 13.4 g (quant.) of crude 3-pentynyl *p*-toluenesulfonate. This tosylate was employed in the next step without further purification. – IR (film): $\tilde{\nu}$ = 1600 cm^{-1} (w, Ar), 1360 (s, $-SO_2-$), 1175 (vs, $-SO_2-$). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.72 (t, *J* = 2.6 Hz, 3H, 5-H), 2.45 (s, 3H, Ar-Me), 2.39–2.58 (m, 2H, 2-H), 4.06 (t, *J* = 7.1 Hz, 2H, 1-H), 7.26–7.86 (m, 4H, Ar-H). – Sodium iodide (25.3 g, 169 mmol) was added to a solution of 3-pentynyl *p*-toluenesulfonate (13.4 g, 56.3 mmol) in dry acetone (150 ml). The mixture was stirred and heated under reflux for 3.5 h, then concentrated in vacuo, poured into water and extracted with pentane. The pentane extracts were washed with water, satd. sodium hydrogen carbonate solution and brine, dried with sodium sulfate, and concentrated in vacuo. The residue was distilled to give 9.23 g (85%) of **4**; b.p. 68–70°C/26 Torr. – n_D^{22} = 1.5172. – IR (film): $\tilde{\nu}$ = 2280 cm^{-1} (w, C≡C), 1170 (vs, C–I), 595 (m, C–I). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.76 (t, *J* = 2.4 Hz, 3H, 5-H), 2.59–2.82 (m, 2H, 2-H), 3.19 (br. t, *J* = 6.8 Hz, 2H, 1-H).

4-Methoxycarbonyl-7-nonyn-3-one (**5**): A mixture of **4** (14.2 g, 72.9 mmol) and DMF (3 drops) was added to a mixture of methyl 3-oxopentanoate (11.1 g, 85.1 mmol) and potassium carbonate (1.40 g, 10.1 mmol) in dry acetone (230 ml). The mixture was stirred and refluxed at 70°C for 12 h. After concentration in vacuo, the mixture was poured into water and extracted with diethyl ether. The ethereal extracts were washed with water, satd. sodium thiosulfate solution, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (200 g). Elution with hexane/ethyl acetate (30:1) gave 8.23 g (58%) of **5**. – n_D^{22} = 1.4595. – IR (film): $\tilde{\nu}$ = 1745 cm^{-1} (s, CO–O), 1715 (s, C=O), 1435 (m, CO–O–Me). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.08 (t, *J* = 7.5 Hz, 3H, 1-H), 1.77 (t, *J* = 2.4 Hz, 3H, 9-H), 1.87–2.25 (m, 4H, 5,6-H), 2.60 (dq, *J* = 1.7, 7.5 Hz, 2H, 2-H), 3.58–3.96 (m, 1H, 4-H), 3.73 (s, 3H, COOMe). – $C_{11}H_{16}O_3$ (196.3): calcd. C 67.32, H 8.22; found C 67.27, H 8.12.

7-Nonyn-3-one (**6**): A solution of **5** (3.36 g, 18.5 mmol) in methanol (10 ml) was added to a stirred solution of lithium hydroxide monohydrate (5.06 g, 121 mmol) in water (90 ml) and methanol (80 ml) and the mixture was heated under reflux at 95°C for 2 h. The resulting white suspension was poured into a satd. ammonium chloride solution and extracted with diethyl ether. The ethereal extracts were washed with water, satd. sodium thiosulfate solution, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was distilled to give 2.33 g of **6** (91%); b.p. 104°C/38 Torr. – n_D^{22} = 1.4511. – IR (film): $\tilde{\nu}$ = 1715 cm^{-1} (vs, C=O). – ^{1}H NMR (90 MHz, $CDCl_3$): δ = 1.06 (t, *J* = 7.4 Hz, 3H, 1-H), 1.77 (t, *J* = 2.4 Hz, 3H, 9-H), 1.59–1.95 (m, 2H, 5-H), 2.08–2.26 (m, 2H, 6-H), 2.45 (q, *J* = 7.4 Hz, 2H, 2-H), 2.53 (t, *J* = 7.0 Hz, 2H, 4-H). – $C_9H_{14}O$: calcd. 138, found 138 (MS). – Due to the high volatility of this compound, its correct elemental analytical data could not be obtained.

2-Ethyl-2-(4'-hexynyl)-5,5-dimethyl-1,3-dioxane (**7**): A solution of **6** (7.75 g, 56.1 mmol) and 2,2-dimethyl-1,3-propanediol (6.30 g, 60.5 mmol) in benzene (230 ml) containing *p*-toluenesulfonic acid monohydrate (0.1 g) was refluxed at 95°C for 24 h, in an apparatus fitted with a Dean-Stark head. The reaction mixture was filtered through Florisil, and the filtrate was washed with satd. sodium hy-

drogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (300 g). Elution with *n*-hexane/ethyl acetate (40:1) gave 294 mg of recovered **6** (4%) and 11.2 g (93%, based on consumed **6**) of **7**. – n_D^{21} = 1.4640. – IR (film): $\tilde{\nu}$ = 1095 cm^{-1} (vs, C–O–C). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.91 (t, *J* = 7.1 Hz, 3H, 2″-H), 0.95 (s, 6H, 5-CH_3), 1.43–1.91 (m, 6H, 1′,2′,1″-H), 1.78 (t, *J* = 2.5 Hz, 3H, 6′-H), 2.08–2.22 (m, 2H, 3′-H), 3.48 (s, 4H, 4,6-H). – $C_{14}H_{24}O_2$ (224.3): calcd. C 74.95, H 10.78; found C 74.94, H 11.08.

Methyl 4-Oxohexanoate (**11**): Zinc/copper couple (28 g, 43 mmol) and succinic anhydride (**8**) (20.0 g, 200 mmol) were suspended in dry DMF (150 ml) and stirred vigorously. Ethyl 2-bromopropanoate (35 ml, *d* = 1.394 g/ml, 269 mmol) in dry DMF (110 ml) was carefully added to this suspension in a dropwise manner, such that the temperature remained below 80 °C. After stirring for 10 h at room temp., the suspension was poured into 2.5 M hydrochloric acid (200 ml) and filtered through Florisil to give a crude solution (400 ml). Concentrated hydrochloric acid (250 ml) and water (50 ml) were added to this solution and the mixture was stirred under reflux for 2.5 h. After cooling to room temp., the solution was saturated with ammonium sulfate and extracted with diethyl ether. The ethereal extracts were washed with water and brine, dried with sodium sulfate and concentrated in vacuo to give crude 4-oxohexanoic acid **10** (50 g). This was used for the next step without further purification. The residue was dissolved in methanol (60 ml) and concentrated sulfuric acid (200 ml), stirred under reflux for 4 h, poured into water, and extracted with diethyl ether. The ethereal extract was washed with water, a 10% sodium thiosulfate solution, water and brine, dried with magnesium sulfate and concentrated in vacuo to give 15 g of crude products. The residue was chromatographed on silica gel (150 g). Elution with pentane/diethyl ether (20:1–10:1) gave 5.40 g (19%) of **11** in 3 steps. – IR (film): $\tilde{\nu}$ = 1750 cm^{-1} (s, C=O), 1720 (s, C=O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 1.10 (t, *J* = 7.4 Hz, 3H, 6-H), 2.52 (q, *J* = 7.4 Hz, 2H, 5-H), 2.59 (t, *J* = 3.0 Hz, 2H, 3-H), 2.65 (t, *J* = 3.0 Hz, 2H, 2-H), 3.67 (s, 3H, OMe). This crude **11** was employed in the next step without further purification.

2-Ethyl-2-(2′-methoxycarbonylethyl)-5,5-dimethyl-1,3-dioxane (**12**): Oxo ester **11** (5.38 g, 37.4 mmol) and 2,2-dimethyl-1,3-propanediol (6.23 g, 59.9 mmol) were dissolved in dry benzene (100 ml). To this was added *p*-toluenesulfonic acid monohydrate (0.50 g, 2.6 mmol), and the mixture was stirred and heated under reflux for 15 h. Water was azeotropically removed by the use of molecular sieve, type 4 Å. After cooling to room temp., the solution was poured into water and extracted with diethyl ether. The ethereal extracts were washed with water, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (100 g). Elution with pentane/diethyl ether (10:1) gave 6.00 g (70%) of **12**; b.p. 120–122 °C/12 Torr. – n_D^{20} = 1.4491. – IR (film): $\tilde{\nu}$ = 1740 cm^{-1} (s, C=O), 1060 (m, C–O), 1030 (s, C–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.89 (s, 3H, 5-Me), 0.90 (t, *J* = 7.4 Hz, 3H, 2′-H), 1.00 (s, 3H, 5-Me), 1.6–1.9 (m, 6H, 1′,1″,2″-H), 3.49 (br. s, 4H, 4,6-H), 3.61 (s, 3H, OCH_3). – $C_{12}H_{22}O_4$ (230.3): calcd. C 62.58, H 9.63; found C 62.46, H 9.60.

2-Ethyl-2-(3′-hydroxypropyl)-5,5-dimethyl-1,3-dioxane (**13**): To a suspension of lithium tetrahydroaluminate (0.57 g, 15 mmol) in dry diethyl ether (10 ml), the ester **12** (1.76 g, 7.65 mmol) in dry diethyl ether (10 ml) was added dropwise and the suspension was stirred at room temp. for 1 h. Water (0.6 ml), a 15% sodium hydroxide solution (0.6 ml) and further water (1.8 ml) were added, and the mixture was filtered. The filter cake was washed with diethyl ether, and the combined ether solutions were concentrated in vacuo. The residue was chromatographed on silica gel (30 g). Elution with pentane/diethyl ether (5:1) gave 1.53 g (99%) of **13**; b.p. 115 °C/3 Torr. – n_D^{20} = 1.4590. – IR (film): $\tilde{\nu}$ = 3390 cm^{-1} (m, O–H), 1090 (s, C–O–C), 1050 (s, C–O). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.89 (br. s, 3H, 5-Me), 0.90 (t, *J* = 7.4 Hz, 3H, 2′-H), 1.03 (s, 3H, 5-Me), 1.6–1.9 (m, 6H, 1′,1″,2″-H), 3.49 (br. s, 4H, 4,6-H), 3.64 (m, 2H, 3″-H). – $C_{11}H_{22}O_3$ (202.3): calcd. C 65.31, H 10.96; found C 64.98, H 10.97.

2-Ethyl-2-(3′-iodopropyl)-5,5-dimethyl-1,3-dioxane (**14**): *p*-Toluenesulfonyl chloride (8.46 g, 44.5 mmol) was added to a solution of **13** (6.36 g, 31.5 mmol) in pyridine (75 ml). The solution was stirred at 4 °C for 10 h. Then water was added slowly, in a dropwise manner, to the solution at 0 °C and the mixture was extracted with diethyl ether. The ethereal extract was washed with satd. copper(II) sulfate solution, water, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate and concentrated in vacuo to give 10.2 g of the crude tosylate. Sodium hydrogen carbonate (3.85 g, 45.8 mmol) and sodium iodide (8.52 g, 38.8 mmol) were then added to a solution of the crude tosylate (10.2 g, 30.1 mmol) in dry acetone (75 ml). The mixture was stirred and heated under reflux for 3 h and extracted with pentane. The extracts were washed with water, a 10% sodium thiosulfate solution, stad. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (100 g). Elution with pentane/diethyl ether (20:1) gave 8.16 g (83%) of **14**; b.p. 98 °C/0.5 Torr. – IR (film): $\tilde{\nu}$ = 1176 cm^{-1} (s, C–I), 1095 (m, C–O–C). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.4 Hz, 3H, 2′-H), 0.91 (br. s, 3H, 5-Me), 0.98 (s, 3H, 5-Me), 1.7–2.1 (m, 2H, 2″-H), 1.74 (q, *J* = 7.4 Hz, 2H, 1″-H), 1.81 (t, *J* = 6.2 Hz, 3″-H), 3.23 (t, *J* = 6.6 Hz, 2H, 3″-H), 3.46 (br. s, 4H, 4,6-H). – This was employed in the next step without further purification.

2-Ethyl-2-(4′-hexynyl)-5,5-dimethyl-1,3-dioxane (**7**): Propyne gas (5.96 g, 149 mmol) was dissolved in dry THF (20 ml) below −40 °C under Ar. It was stirred for 10 min below −50 °C and then *n*BuLi in hexane (1.60 M, 10 ml, 16 mmol) was slowly added to the solution in a dropwise manner. It was then stirred for 10 min below −50 °C, HMPA (4.5 ml) was added dropwise, and the mixture was stirred for a further 30 min below −50 °C. Then, a second portion of *n*BuLi in hexane (1.60 M, 10 ml, 16 mmol) was slowly added to the solution. After that, it was stirred for 10 min below −50 °C. A solution of **14** (4.35 g, 13.9 mmol) in dry THF (50 ml) was added dropwise to this solution at −50 °C to −40 °C and the temperature was gradually allowed to rise to room temp. After stirring for 3 h at room temp., the mixture was poured into ice-cooled satd. ammonium chloride solution and extracted with diethyl ether. The ethereal extracts were washed with satd. ammonium chloride solution, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate and concentrated in vacuo. The residue was chromatographed on silica gel (50 g). Elution with pentane/diethyl ether (25:1) gave 2.17 g of alkyne **7** (70%). – Its IR and ^1H-NMR spectra were identical with those of the authentic **7**.

(E)-2-Ethyl-2-(4′-hexenyl)-5,5-dimethyl-1,3-dioxane (**15**): A solution of **7** (3.00 g, 13.4 mmol) in THF (10 ml) was added dropwise under nitrogen to a stirred solution of lithium (1.70 g, 225 mmol) in ethylamine (100 g) at −78 °C, and the temperature was gradually raised to −20 °C over a period of 3 h. After quenching with methanol and a satd. ammonium chloride solution, the resulting mixture was extracted with diethyl ether. The ethereal extracts were washed with water, satd. sodium hydrogen carbonate

solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was purified by chromatography on silica gel (50 g). Elution with *n*-hexane/ethyl acetate (100:1) gave **15** (3.01 g, 99%). n_D^{21} = 1.4523. – IR (film): $\tilde{\nu}$ = 1095 cm^{-1} (vs, C–O–C). – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.7 Hz, 3H, 3″-H), 0.93 (s, 3H, 5-Me), 0.95 (s, 3H, 5-Me), 1.28–1.86 (m, 9H, 1′,2′,6′,1″-H), 1.88–2.09 (m, 2H, 3′-H), 3.46 (s, 4H, 4,6-H), 5.36–5.49 (m, 2H, CH=CH). – ^{13}C NMR (22.5 MHz): δ = 7.6, 17.9, 22.7, 22.8, 23.1, 26.1, 29.8, 32.8, 70.0, 100.6, 125.0, 131.2. – $C_{14}H_{26}O_2$ (226.4): calcd. C 74.29, H 11.58; found C 73.98, H 11.44.

(4′S,5′S)-2-Ethyl-2-(4′,5′-dihydroxyhexyl)-5,5-dimethyl-1,3-dioxane (**16**): To a solution of AD-mix α® (15.6 g) and methanesulfonamide (1.05 g, 11.1 mmol) in water (55 ml) and 2-methyl-2-propanol (40 ml), a solution of **8** (2.49 g, 11.0 mmol) in 2-methyl-2-propanol (15 ml) was added dropwise at 0 °C and the solution was stirred for 9 h at 4 °C. The reaction was quenched at 0 °C by the addition of sodium sulfite heptahydrate (3.3 g). The reaction mixture was then warmed to room temp., stirred for 30 min, and extracted with ethyl acetate. The combined extracts were washed with a 1.5 M potassium hydroxide solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (40 g). Elution with *n*-hexane/ethyl acetate (5:1) gave 2.72 g (95%) of **16**. – n_D^{22} = 1.4692. – $[\alpha]_D^{23}$ = –14.3 (*c* = 0.86, MeOH). – IR (film): $\tilde{\nu}$ = 3410 cm^{-1} (m, O–H), 1095 (vs, C–O–C). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.5 Hz, 3H, 2″-H), 0.90 (s, 3H, 5-Me), 1.00 (s, 3H, 5-Me), 1.18 (d, *J* = 6.2 Hz, 3H, 6′-H), 1.33–1.89 (m, 8H, 1′,2′,3′,1″-H), 2.23, 2.31 (each d, *J* = 4.2, 4.8 Hz, 2H, 4′,5′-OH), 3.29–3.70 (m, 4H, 4,5-H), 3.22–3.68 (m, 2H, 4′,5′-H). – $C_{14}H_{28}O_4$ (260.4): calcd. C 64.58, H 10.84; found C 64.14, H 10.97. – A portion of **16** was converted into the corresponding bis[(*R*)-MTPA] ester in the conventional manner. HPLC analysis of the MTPA ester on a Senshu pak® [silica-1251-N 4.6 × 250 mm, hexane/tetrahydrofuran (20:1), 1.0 ml/min]: t_R = 25.0 min {bis[(*R*)-MTPA] ester of (*S,S*)-**16**; 88.3%}, 30.0 min {bis[(*R*)-MTPA] ester of (*R,R*)-**16**; 11.7%}. – The enantiomeric purity of (*S,S*)-**16** was determined to be 77% e.e.

(4′S,5′S)-2-Ethyl-5,5-dimethyl-2-[4′,5′-bis(3,5-dinitrobenzoyloxy)hexyl]-1,3-dioxane (**17**): To a solution of **16** (77% e.e., 2.41 g, 9.24 mmol) in dry pyridine (5 ml) and dry dichloromethane (20 ml) at 0 °C, 3,5-dinitrobenzoyl chloride (4.80 g, 20.8 mmol) and DMAP (5 mg) were added and the mixture was stirred at room temp. for 3 d. Then the mixture was poured into water and extracted with dichloromethane. The combined extracts were washed with satd. copper(II) sulfate solution, water, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (120 g). Elution with ethyl acetate gave **17** which was purified by recrystallization from dichloromethane/*n*-hexane to give 4.09 g (68%) of **17** as colorless neddles. The crystals obtained were recrystallized from dichloromethane/*n*-hexane again to give 3.53 g (59%) of **17**; m.p. 129–131 °C. – $[\alpha]_D^{25}$ = –9.94 (*c* = 0.65, $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 1725 cm^{-1} (vs, CO–O), 1550 (vs, Ar–NO_2), 1345 (vs, Ar–NO_2), 1095 (s, C–O–C). – ^1H NMR (270 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.4 Hz, 3H, 2″-H), 0.84, 0.99 (each s, 6H, 5-Me), 1.52 (d, *J* = 5.9 Hz, 3H, 6′-H), 1.56–1.65 (m, 2H, 2″-H), 1.68–1.78 (m, 4H, 1′,1″-H), 1.87–1.97 (m, 2H, 3′-H), 3.34, 3.35 (each br. d, *J* = 10.7 Hz, 2H, 4,5-H_{eq}), 3.51, 3.52 (each d, *J* = 11.6 Hz, 2H, 4,5-H_{ax}), 5.47–5.58 (m, 2H, 4′,5′-H), 9.10–9.23 (m, 6H, Ar-H). – $C_{28}H_{32}O_{14}N_4$ (648.6): calcd. C 51.85, H 4.97, N 8.64; found C 51.48, H 4.66, N 8.47.

(4′S,5′S)-2-Ethyl-2-(4′,5′-dihydroxyhexyl)-5,5-dimethyl-1,3-dioxane (**16**): To a stirred solution of **17** (1.26 g, 1.94 mmol) in methanol (35 ml), potassium carbonate (3.50 g, 25.3 mmol) was added and the mixture was stirred at room temp. for 3 h. Subsequently, the mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed with satd. ammonium chloride solution, water, satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (15 g). Elution with *n*-hexane/ethyl acetate (5:1) gave 469 mg (92%) of **16**. – $[\alpha]_D^{25}$ = –18.8 (*c* = 1.02, MeOH). – Its IR and ^1H-NMR spectra were identical to those of enantiomerically impure **9**. In almost the same manner as described above, the enantiomeric purity was determined to be 99.4% e.e.

(1S,5R,7S)-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane [(–)-*exo*-Isobrevicomin] (**1**): A solution of **16** (900 mg, 3.46 mmol) in dilute hydrochloric acid (30 ml) was stirred at room temp. for 2 h and extracted with diethyl ether. The ethereal extracts were washed with satd. sodium hydrogen carbonate solution and brine, dried with potassium carbonate, and concentrated in vacuo. The residue was chromatographed on Al_2O_3 (10 g). Elution with pentane gave **1** (420 mg) which was purified by distillation to give pure **1** (337 mg, 64%); b.p. 75 °C/25 Torr. – n_D^{23} = 1.4424. – $[\alpha]_D^{22}$ = –60.4 (*c* = 1.16, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2945 cm^{-1} (s), 1465 (m), 1360 (m), 1340 (m), 1240 (m), 1225 (m), 1180 (s), 1135 (m), 1105 (m), 1075 (m), 1060 (m), 1015 (vs), 980 (m), 925 (s), 905 (s), 865 (m), 855 (m). – ^1H NMR (500 MHz, C_6D_6): δ = 1.03–1.09 (m, 1H, 2-H_{eq}), 1.08 (t, *J* = 7.5 Hz, 3H, 2′-H), 1.09 (d, *J* = 6.1 Hz, 3H, 7-Me), 1.34–1.40 (m, 1H, 3-H_{eq}), 1.46–1.49 (m, 2H, 4-H), 1.58 (dddd, *J* = 13.1, 13.1, 5.4, 3.1 Hz, 1H, 2-H_{ax}), 1.69–1.83 (m, 3H, 1′-H and 3-H_{ax}), 3.74–3.76 (m, 1H, 1-H), 3.93 (q, *J* = 6.5 Hz, 1H, 7-H). – ^{13}C NMR (67.8 MHz): δ = 8.1, 18.0, 22.2, 28.7, 31.5, 34.4, 75.9, 80.3, 109.9. – $C_9H_{16}O_2$ (156.2): calcd. C 69.16, H 10.32; found C 69.07, H 10.31; calcd. 156.1151, found 156.1145 (HR MS).

(Z)-2-Ethyl-2-(4-hexenyl)-5,5-dimethyl-1,3-dioxane (**18**): Nickel diacetate tetrahydrate (0.57 g, 2.30 mmol) was added to a suspension of BER (borohydride exchange resin) (7.65 g) in methanol (160 ml) at room temperature under hydrogen. Immediately, a black coating of nickel boride was observed and then a solution of **7** (5.11 g, 22.8 mmol) in methanol (20 ml) was added at 0 °C. The mixture was stirred for 3 h, filtered through Celite, and poured into water. The resulting mixture was extracted with diethyl ether. The combined ethereal extracts were washed with satd. sodium hydrogen carbonate solution and brine, dried with potassium carbonate and concentrated in vacuo. The residue was chromatographed on silica gel (80 g). Elution with *n*-hexane/ethyl acetate (100:1) gave 5.03 g (97%) of **18**. – n_D^{21} = 1.4568. – IR (film): $\tilde{\nu}$ = 1655 cm^{-1} (vw, C=C), 1095 (vs, C–O–C). – ^1H NMR (270 MHz, $CDCl_3$): δ = 0.88 (t, *J* = 7.7 Hz, 3H, 2″-H), 0.93 (s, 3H, 5-Me), 0.95 (s, 3H, 5-Me), 1.28–1.86 (m, 9H, 1′,2′,6′,1″-H), 1.88–2.09 (m, 2H, 3′-H), 3.46 (s, 4H, 4, 6-H), 5.36–5.49 (m, 2H, CH=CH). – ^{13}C NMR (22.5 MHz): δ = 7.5, 12.7, 22.6, 22.7, 23.0, 26.0, 26.9, 29.7, 32.8, 69.9, 100.5, 124.0, 130.4. – $C_{14}H_{26}O_2$ (226.4): calcd. C 74.29, H 11.58; found C 74.30, H 11.32.

(4′S,5′R)-2-Ethyl-2-(4′,5′-dihydroxyhexyl)-5,5-dimethyl-1,3-dioxane (**19**): To a solution of AD-mix-α® (4.46 g) and methanesulfonamide (280 mg, 3.01 mmol) in water (15 ml) and 2-methyl-2-propanol (12 ml), a solution of **7** (662 mg, 2.92 mmol) in 2-methyl-2-propanol (3 ml) was added dropwise at 0 °C, and the mixture was stirred for 6 h at 4 °C. The reaction was quenched at 0 °C by the addition of sodium sulfite heptahydrate (3.3 g) and then the mixture was warmed to room temp., stirred for 30 min, and extracted with ethyl acetate. The combined extracts were washed with a 1.5 M potassium hydroxide solution and brine, dried with magnesium

sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (15 g). Elution with *n*-hexane/ethyl acetate (5:1) gave 715 mg (94%) of **12**. – n_D^{24} = 1.4690. – $[\alpha]_D^{26}$ = −3.09 (*c* = 0.99, MeOH). – IR (film): $\tilde{\nu}$ = 3415 cm^{-1} (s, O−H), 1095 (vs, C−O−C). – ^1H NMR (90 MHz, $CDCl_3$): δ = 0.89 (t, *J* = 7.4 Hz, 3H, 2″-H), 0.91, 1.00 (each s, 6H, 5-Me), 1.15 (d, *J* = 6.4 Hz, 3H, 6′-H), 1.30−1.48 (m, 2H, 2′-H), 1.66−1.88 (m, 4H, 1′,1″-H), 2.03, 2.22 (each d, 2H, 4′,5′-OH), 3.48 (s, 4H, 4,6-H), 3.27−3.88 (m, 4H, 4′,5′-H). – $C_{14}H_{28}O_4$ (260.4): calcd. C 64.58, H 10.84; found C 64.15, H 10.58. – A portion of **19** was converted into the corresponding bis[(*R*)-MTPA] ester in the conventional manner. HPLC analysis of the bis[(*R*)-MTPA] ester of **19** on a Senshu Pak® [silica-1251-N 4.6 × 250 mm, hexane/tetrahydrofuran (30:1), 0.8 ml/min]: t_R = 45 min {bis[(*R*)-MTPA] ester of (*S*,*R*)-**19**; 57.4%}, 54 min {bis[(*R*)-MTPA] ester of (*R*,*S*)-**19**; 42.6%}. – The enantiomeric purity of (*S*,*R*)-**19** was determined to be 15% e.e.

Immobilization of Lipase PS: Lipase PS (Amano) (3 g) was mixed with Hyflo Super Cell® (10 g). Then, 0.1 M potassium phosphate buffer (pH = 7, 10 ml) was added, the mixture was shaken vigorously, and dried in vacuo (30 h, 4 Torr).

Purification of Optically Impure **19** *with Immobilized Lipase PS:* A mixture containing enantiomerically impure **19** (15% e.e., 1.81 g, 6.95 mmol), vinyl acetate (6.63 g, 75.8 mmol), *tert*-butyl methyl ether (93 ml), and immobilized lipase PS (13.0 g) was stirred at room temp. for 1 h. It was then filtered and the filter cake was washed several times with diethyl ether. The filtrate was washed with satd. sodium hydrogen carbonate solution and brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel. Elution with *n*-hexane/ethyl acetate (7:1) gave a mixture of **21** and **22** (1.23 g). To a solution of this mixture (1.23 g) in methanol (15 ml), potassium carbonate (1.02 g, 7.38 mmol) was added at room temp. After 10 h, the mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed with brine, dried with magnesium sulfate, and concentrated in vacuo. The residue was chromatographed on silica gel (30 g). Elution with *n*-hexane/ethyl acetate (7:1) gave 958 mg of **19** [53% (2 steps)]. – $[\alpha]_D^{24}$ = −13.4 (*c* = 1.05, MeOH). – In the same manner as described above, the enantiomeric purity was determined to be 86% e.e.

Second Acetylation to Enrich the Enantiomeric Purity of Partially Resolved Diol **19**: In almost the same manner as described above, the partially resolved **19** (929 mg, 3.57 mmol, 86% e.e.) was treated with immobilized lipase PS (6.04 g), vinyl acetate (3.40 g, 38.9 mmol) and *tert*-butyl methyl ether (47.7 ml) for 45 min at room temp. to give 953 mg of the acetates **21** and **22**. After methanolysis by treatment with potassium carbonate (0.75 g, 5.43 mmol) in methanol (10 ml), 615 mg of **19** [77% (2 steps)] was obtained. – $[\alpha]_D^{26}$ = −19.1 (*c* = 1.04, MeOH). – Its IR and ^1H-NMR spectra were identical with those of **19**. In the same manner as described above, the enantiomeric purity was determined to be 98% e.e.

(1S,5R,7R)-5-Ethyl-7-methyl-6,8-dioxabicyclo[3.2.1]octane [(−)-*endo*-Isobrevicomin] (**2**): A solution of **19** (0.673 g, 2.58 mmol) in dilute hydrochloric acid (30 ml) was stirred at room temp. for 2 h, and extracted with diethyl ether. The ethereal extracts were washed with satd. sodium hydrogen carbonate solution and brine, dried with potassium carbonate and concentrated in vacuo. The residue was chromatographed on Al_2O_3 (10 g). Elution with pentane gave **2** (281 mg) which was purified by distillation to give 112 mg of pure **2** (28%); b.p. 74 °C/24 Torr. – n_D^{24} = 1.4476. – $[\alpha]_D^{26}$ = −88.1 (*c* = 1.16, $CHCl_3$). – IR (film): $\tilde{\nu}$ = 2940 (s), 2880 (m), 1465 (m), 1370 (m), 1340 (m), 1180 (m), 1135 (m), 1100 (s), 1025 (vs, C−O−C), 975 (w), 915 (s), 900 (s), 855 (m). – ^1H NMR (270 MHz, C_6D_6): δ = 1.06 (d, *J* = 6.6 Hz, 3H, 7-Me), 1.10 (t, *J* = 7.4 Hz, 3H, 5-CH_2CH_3), 1.19−1.28 (m, 1H, 2-H_{eq}), 1.29−1.39 (m, 1H, 3-H_{eq}), 1.46−1.67 (m, 3H, 4-H, 2-H_{ax}), 1.76 (q, *J* = 7.4 Hz, 2H, 5-CH_2CH_3), 1.81−1.93 (m, 1H, 3-H_{ax}), 3.82−3.85 (m, 1H, 1-H), 4.07 (ddq, *J* = 1.1, 4.2, 6.6 Hz, 1H, 7-H). – ^{13}C NMR (67.8 MHz): δ = 7.5, 13.9, 17.8, 24.3, 31.5, 33.1, 76.0, 77.2, 108.7. – $C_9H_{16}O_2$: calcd. 156.1151, found 156.1153 (HRMS).

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